Serial No.: 08/873,601
Filed: June 12,1997

REMARKS

Claims 1-8, 27, 28, 31, 32, 34, 39 and 43 are pending. Claims 1-8, 27, 28, 31, 32, 34, 39 are cancelled by the present Amendment in preference of nearly identical new Claims 44-57. Newly added Claims 43-57 recite "A cell containing a composition comprising . . .", thereby definitively placing these claims in the originally elected group, namely Group I.

Support for newly added Claims 44-57 can be found in originally filed Claims 1-8, 27, 28, 31, 32, 34, 39 respectively.

Support for the recitation in Claims 44 and 45 "wherein said enzymes do not biologically react with said scaffold" can be found throughout the specification, for example at 4:4-5 and in originally filed Claim 21. Support for the recitation in new Claims 44 and 45 "capable of being bound" can be found in originally-filed Claim 2 and throughout the specification, for example at 3:11-12. Support for the recitation in new Claim 51 "wherein said agent precursor is from a library of synthetic compounds" can be found throughout the specification, for example at 34:18-19.

No new matter has been introduced by way of the newly added claims, and entry thereof is respectfully requested. A copy of the pending claims, after entry of the present Amendment, is attached hereto for the Examiner's convenience..

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1-8, 27-28, 31-32, 34, and 39 stand rejected under 35 U.S.C. § 112, first paragraph for reciting "exogenous scaffolds having no enzymatic activity". Newly added Claims 44-57 do not contain the language "having no enzymatic activity". Applicants submit that the Claims 44-57 conform to the requirement of 35 U.S.C. §112, first paragraph.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1-8, 27-28, 31-32, 34, and 39 stand rejected under 35 U.S.C. § 112, second paragraph.

The Examiner considers Claim 8 as indefinite for reciting "an exogenous bioactive agent precursor" and states that it is not possible to determine what is or is not "a bioactive agent precursor". Without admitting the propriety of the rejection, Applicants added new

Serial No.: 08/873,601
Filed: June 12,1997

Claim 51 containing the recitation "an exogenous bioactive agent precursor, wherein said agent precursor is from a library of synthetic compounds." Applicants submit that the metes and bounds of a 'library of synthetic compounds' is known to the skilled artisan.

Claims 31, 32, 34, and 39 stand rejected under 35 U.S.C. § 112, second paragraph as being vague and indefinite for reciting the term "fusion partner". Applicants have added new Claims 54-57 to replace Claims 31, 32, 34, and 35, and respectfully submit that the definition of the term "fusion partner" is found both implicitly and explicitly within the specification (*see, e.g.*, 16:15 26), and therefore is not vague or indefinite.

> In addition to the coding sequences for the scaffolds and enzymes, the nucleic acids of the invention may include fusion partners. By "fusion partner" herein is meant a sequence that is associated either with the nucleic acid or the expression product that confers a common function or ability. Fusion partners can be heterologous (i.e. not native to the host cell), or synthetic (not native to any cell). Suitable fusion partners include, but are not limited to: 1) targeting sequences, defined below, which allow the localization of the scaffolds and enzymes into a subcellular or extracellular compartment; 2) rescue sequences, as defined below, which allow the purification or isolation of either the scaffolds and enzymes or the nucleic acids encoding them; 3) stability sequences, which confer stability or protection from degradation to the scaffolds and enzymes or the nucleic acids encoding them, for example resistance to proteolytic degradation; or 4) combinations of any of 1), 2) and 3).

Moreover, the specification discloses several examples of fusion partners, *e.g.*, targeting sequences (16:27-22:11), rescue sequences (22:12-22), stability conferring sequences (22:23-23:3), and linker or tethering sequences (23:6-23). In addition the specification states:

> The fusion partners may be placed anywhere (i.e. N-terminal, C-terminal, internal) in the structure as the biology and activity permits.

23:4-5.

> In a preferred embodiment, combinations of fusion partners are used. Thus, for example, any number of combinations may be used, with or without linker sequences. As is described herein, using a base vector that contains a cloning site for receiving the enzyme and/or scaffold coding regions, one can cassette in various fusion partners 5' and 3' of the coding region.

23:24-28.

Thus, given the specification, a skilled artisan will appreciate what is meant by the

term "fusion partner" as that term is used within the context of the specification and the claims. Accordingly, Applicants respectfully submit that the skilled artisan understands what is encompassed by the claims, and can identify the subject matter as claimed.

Claims 1-8, 27-28, 31-32, 34, and 39 stand rejected under 35 U.S.C. § 112, second paragraph as being vague and indefinite for reciting the term "exogenous scaffold." Applicants respectfully disagree.

The definition of "exogenous scaffold", recited by new Claims 44-57, can be found both implicitly and explicitly throughout the specification. For example the specification states:

> When the novel compositions are introduced into cells as is outlined below, the scaffolds are preferably exogeneous scaffolds. By "exogeneous scaffold" herein is meant that the scaffold either a) does not naturally occur within the cell, or b) does naturally occur within the cell but is present at a either a significantly higher concentration than is normally seen within the cell or in a form not normally seen in the cell; e.g. is a portion of a naturally occurring protein or nucleic acid sequence. In a preferred embodiment, the exogeneous scaffolds are synthetic; i.e. they do not naturally occur in nature. In some embodiments, it may be possible to alter endogeneous scaffolds such as actin chemically to produce novel scaffolds.

13:11-19.

Moreover, the specification discloses the binding of enzymes to the scaffold, and the kind of enzymes that can be used to bind to the scaffold. *See, e.g.*, 13:20-16:14.

Therefore, given the specification, a skilled artisan will appreciate what is meant by the term "exogenous scaffold", as that term is used within the context of the specification and the claims. Accordingly, Applicants respectfully submit that the skilled artisan understands what is encompassed by the claims, and can identify the subject matter as claimed.

In light of the comments provided herein, Applicants respectfully submit that new Claims 44-57 meet all the requirements of 35 U.S.C. § 112.

Rejections Under 35 U.S.C. §101

Claims 1-8, 27-28, 31-32, 34, and 39 stand rejected under 35 U.S.C. § 101 as being directed to non-statutory subject matter.

Applicants respectfully submit that new Claims 44-57 cover 35 U.S.C. § 101 statutory

subject matter.

Rejections Under 35 U.S.C. §102(e)

Claims 1-8, 27-28, 31-32, 34, and 39 stand rejected under 35 U.S.C. § 102(c) as being anticipated by United States Patent Number 5,672,491 to Khosla *et al.* ("Khosla *et al.*"). Without admitting the propriety of the rejection, Applicants have added new Claims 44-57 that recite, *inter alia*, "wherein said enzymes do not biologically react with said scaffold."

As argued previously, Khosla *et al.* teach the synthesis of polyketides by the multi-enzyme complex 6-deoxyerythronolide B synthetase (DEBS) consisting of three different proteins. The authors construct expression vectors encoding these three proteins, introduce them into host cells (which do not contain the corresponding endogenous genes), and demonstrate that polyketides are made. Figure 9 of Khosla *et al.* shows the gene organization and the modular structure for the three proteins which constitute the multi-enzyme complex DEBS.

The Examiner interprets the disclosure of Khosla *et al.* as evidence that the three proteins bind or interact with each other to form DEBS. The Examiner argues that one of the three proteins functions as a scaffold, and therefore, provides binding sites for the other two proteins. As such, the Examiner contends that the subject matter of the claims is anticipated by Khosla *et al.* Applicants respectfully disagree.

First of all, while Khosla *et al.* express the three proteins and demonstrate enzymatic activity, they do not demonstrate that the three recombinant proteins assemble into a multi-enzyme complex comprising the three proteins. That is, the structure of the DEBS multi-enzyme complex has not been determined yet. Thus, contrary to the Examiner's assumption, it is not known if one of the three proteins provides binding sites for the other two proteins. It is equally likely that protein 1 provides a binding site for protein 2 and protein 2 provides a binding site for protein 3. In this scenario, whichever protein is considered a scaffold, this scaffold does not provide "at least a first binding site and a second binding site" to which a "first enzyme" and a "second enzyme" can bind, as recited in the claims.

As the Examiner is aware, inherency is not a permissive consideration on which to base obviousness. "That which may be inherent is not necessarily known. Obviousness

cannot be predicted on what is unknown." *In re Spormann*, 150 USPQ 449, 452 (CCPA 1966).

Secondly, as is known in the art, the DEBS multi-enzyme complex consists of three proteins, each comprising modules. Each of the proteins adds two-carbon building blocks to the polyketide and performs chemical modification to the chain before transferring it to the next part of the enzyme (see also Figure 9 in Khosla *et al.*). Even assuming, arguendo, that one protein of the DEBS complex (protein 1) provides at least a first binding site for protein 2 and a second binding site for protein 3, such a complex is not anticipated by the claims as amended. Within the DEBS complex, protein 2 or protein 3 or both (which, according to the Examiner's interpretation, correspond to enzymes 1 and 2 of the instant application) biologically react with protein 1 (which, according to the Examiner's interpretation, corresponds to the scaffold of the instant application) by accepting a substrate for further modification. This is not the case in the present invention. The amended claims clearly recite that the enzymes, which bind to the scaffold, do not biologically react with said scaffold.

Accordingly, Applicants respectfully submit that Claims 14 57 are not anticipated by Khosla *et al.*

Rejections Under 35 U.S.C. §102(b)

Claims 1-8, 27-28, 31 32, 34, and 39 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Horowitz as evidenced by the teachings of Zhao and Padmanabahn (New Biol. 1991).

Horowitz teaches adenoviruses that infect mammalian cells. The Examiner's position appears to be that adenoviral genome is an exogenous scaffold, having binding sites, for example for adenoviral DNA and RNA polymerases. However, even assuming arguendo that this could be true, both the DNA polymerase and the RNA polymerase are enzymes that biologically react with the adenoviral genome: the DNA polymerase biologically reacts with the adenoviral genome to produce DNA copies and the RNA polymerase biologically reacts with the adenoviral genome to produce mRNAs encoding adenoviral proteins.

Zhao and Padmanabahn (New Biol. 1991) disclose three basic amino acid clusters in

the adenovirus DNA polymerase, designated BS I, BS II, and BS III, respectively. These clusters comprise a novel bipartite nuclear localization signal, which, when fused to a heterologous protein such as E. coli beta galactosidase, targeted the fusion protein to the nucleus.

For an invention to be anticipated under 35 U.S.C. §102(b), the cited reference must teach "each and every element" of the claim (MPEP §2131).

Applicants submit that new Claims 44 and 45 and the respective dependent claims are not anticipated by the references cited. The references do not teach that the enzymes do not biologically interact with an exogenous scaffold. Accordingly, Applicants respectfully submit that new Claims 44-57 are not anticipated by either Zhao or Padmanabahn.

Additional Points Raised By The Examiner

Examiner's point #17 is unclear. Based upon Applicants' detailed response to the previous Office Action, in which claims 1-8 were rejected under §103(a) over Bott *et al.* and the fact that the Examiner did not reinstate this rejection, it is Applicants' belief that this rejection is overcome.

Examiner's point #18, referring to the Ricard *et al.* reference is noted by the Applicants. However, as no complete reference was provided and no objection/rejection was raised based upon this reference. Accordingly Applicants provide no further comments regarding this reference.

Examiner's point #19, referring to the identical disclosure in WO 95/08548 and US 5,672,491 is noted by the Applicants.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and an early notification of such is respectfully solicited.

Serial No.: 08/873,601
Filed: June 12,1997

If after review of this amendment, the Examiner has further unresolved issues, the Examiner is respectfully requested to phone the undersigned, Robin Silva, at (415) 781-1989.

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP

Date: 2 Nov 2000

Brian T. Clarke (Reg. No. 45,552) for
Robin M. Silva (Reg. No. 38,304)

Four Embarcadero Center, Suite 3400
San Francisco, California 94111-4187
Telephone: (415) 781-1989

Serial No.: 08/873,601
Appendix of Pending Claims

44. A cell containing a composition comprising:

(a) an exogenous scaffold comprising at least a first binding site and a second binding site; and

(b) at least a first enzyme and a second enzyme, wherein at least one of said enzymes is heterologous to said cell,

wherein said first enzyme is capable of being bound to said first binding site and said second enzyme is capable of being bound to said second binding site, and wherein said enzymes do not biologically react with said scaffold.

45. A cell containing a composition comprising:

(a) nucleic acid encoding an exogenous scaffold comprising at least a first binding site and a second binding site; and

(b) nucleic acid encoding at least a first enzyme and a second enzyme, wherein at least one of said enzymes is heterologous to said cell,

wherein said first enzyme is capable of being bound to said first binding site and said second enzyme is capable of being bound to said second binding site, and wherein said enzymes do not biologically react with said scaffold..

46. The cell according to Claims 44 or 45, wherein said scaffold comprises at least three binding sites.

47. The cell according to Claims 44 or 45, wherein said scaffold comprises at least four binding sites.

48. The cell according to Claims1 or 2, wherein said scaffold comprises at least five binding sites.

49. The cell according to Claims 44 or 45, wherein said binding sites are on the same scaffold molecule.

Serial No.: 08/873,601
Appendix of Pending Claims

50. The cell according to Claims 44 or 45, wherein said binding sites are on different scaffold molecules.

51. The cell according to Claims 44 or 45, further comprising:

(c) an exogenous bioactive agent precursor, wherein said agent precursor is from a library of synthetic compounds.

52. The cell according to Claims 44 or 45, wherein said cell is a mammalian cell.

53. The cell according to Claims 44 or 45, wherein said scaffold is linear.

54. The cell according to Claims 44 or 45, wherein said scaffold further comprises a fusion partner.

55. The cell according to Claims 44 or 45, wherein at least one of said enzymes further comprises a fusion partner.

56. The cell according to Claim 54, wherein said fusion partner is a targeting sequence.

57. The cell according to Claim 55, wherein said fusion partner is a targeting sequence.